Please replace paragraph **[0014]** *as follows*:

[0014] The present invention further provides methods for identifying and designing small molecules that bind to the coactivator binding site using atomic models of nuclear receptors. The method involves modeling test compounds that fit spatially into a nuclear receptor coactivator binding site of interest using an atomic structural model comprising a nuclear receptor coactivator binding site or portion thereof, screening the test compounds in a biological assay characterized by binding of a test compound to a nuclear receptor coactivator binding site, and identifying a test compound that modulates coactivator binding to the nuclear receptor.

Please replace paragraph **[0017]** *as follows*:

[0017] The invention further includes a method for identifying an agonist or antagonist of coactivator binding to a nuclear receptor. The method comprises providing the atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system; modeling compounds which fit spatially into the nuclear receptor coactivator binding site; and identifying in an assay for nuclear receptor activity a compound that increases or decreases activity of the nuclear receptor through binding the coactivator binding site.

Please replace paragraph **[0019]** *as follows*:

[0019] Also provided is a method of identifying a compound that selectively modulates the activity of one type of nuclear receptor compared to other nuclear receptors. The method is exemplified by modeling test compounds that fit spatially and preferentially into a nuclear receptor coactivator binding site of interest using an atomic structural model of a nuclear receptor coactivator binding site, selecting a compound that interacts with one or more residues of the coactivator binding site unique in the context of that site, and identifying in an assay for coactivator binding activity a compound that selectively binds to the coactivator binding site compared to other nuclear receptors. The unique features involved in receptor-selective coactivator binding can be identified by comparing atomic models of different receptors or isoforms of the same type of receptor.

Please replace paragraph **[0044]** *as follows*:

[0044] Compounds that bind to the coactivator binding site of nuclear receptors can be identified by computational modeling and/or screening. For example, coactivator agonists or antagonists can be identified by providing atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system, modeling them, and identifying compounds that fit spatially into the coactivator binding site. By a "portion thereof" is intended the atomic coordinates corresponding to a sufficient number of residues or their atoms of the coactivator binding site that interact with a compound capable of binding to the site. This includes receptor residues having an atom within 4.5Å of a bound compound or fragment thereof. For instance, human TR residues Val284, Phe293, Ile302, Leu305 and Leu454 contain side chain atoms that are within 4.5Å, and interact with, hydrophobic residues of a (SEQ ID NO: 1) LxxLL motif of an NR-box 2 coactivator peptide. As another example, an atomic structural model utilized for computational modeling and/or screening of compounds that bind to the coactivator binding site may include a portion of atomic coordinates of amino acid residues corresponding to the site composed of residues of human thyroid receptor selected from Val284, Lys288, Ile302, Lys306, Leu454 and Glu457, or their structural and functional equivalents found in other receptors. Thus, for example, the atomic coordinates provided to the modeling system can contain atoms of the nuclear receptor LBD, part of the LBD such as atoms corresponding to the coactivator binding site or a subset of atoms useful in the modeling and design of compounds that bind to a coactivator binding site.

Please replace paragraph **[0045]** *as follows*:

[0045] The atomic coordinates of a compound that fits into the coactivator binding site also can be used for modeling to identify compounds or fragments that bind the site. By "modeling" is intended quantitative and qualitative analysis of molecular structure/function based on atomic structural information and receptor-coactivator agonists/antagonists interaction models. This includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models. Modeling is preferably performed using a computer and may be further optimized using known methods.

By "fits spatially" is intended that the three-dimensional structure of a compound is accommodated geometrically by a cavity or pocket of a nuclear receptor coactivator binding site.

Please replace paragraph **[0046]** *as follows*:

[0046] Compounds of particular interest fit spatially and preferentially into the coactivator binding site. By "fits spatially and preferentially" is intended that a compound possesses a three-dimensional structure and conformation for selectively interacting with a nuclear receptor coactivator binding site. Compounds that fit spatially and preferentially into the coactivator binding site interact with amino acid residues forming the hydrophobic cleft of this site. In particular, the hydrophobic cleft of the coactivator binding site comprises a small cluster of hydrophobic residues. The site also contains polar or charged residues at its periphery. The present invention also includes a method for identifying a compound capable of selectively modulating coactivator binding to different nuclear receptors. The method comprises the steps of modeling test compounds that fit spatially and preferentially into the coactivator binding site of a nuclear receptor of interest using an atomic structural model of a nuclear receptor, screening the test compounds in a biological assay for nuclear receptor activity characterized by preferential binding of a test compound to the coactivator binding site of a nuclear receptor, and identifying a test compound that selectively modulates the activity of a nuclear receptor. Such receptor-specific compounds are selected that exploit differences between the coactivator binding sites of one type of receptor versus a second type of receptor, such as the differences depicted in **Figure 19**.

Please replace paragraph **[0071]** *as follows*:

[0071] The machine-readable data storage medium can be used for interactive drug design and molecular replacement studies. For example, a data storage material is encoded with a first set of machine-readable data that can be combined with a second set of machine-readable data. For molecular replacement, the first set of data can comprise a Fourier transform of at least a portion of the structural coordinates of the nuclear receptor or portion thereof of interest, and the second data set comprises an X-ray diffraction pattern of the molecule or molecular complex of interest. Using a machine programmed with instructions for using the

first and second data sets a portion or all of the structure coordinates corresponding to the second data can be determined.

Please replace paragraph **[0146]** *as follows*:

Several peptides containing GRIP1 NR-box 2 were tested in crystallization trials with the hTRβ LBD. The complex of the hTRβ LBD with the GRIP1 NR-box 2 peptide 686-KHKILHRLLQDSS-698 (residues 12-24 of SEQ ID NO: 6) produced crystals that were dependent on both the presence and the concentration of the peptide. Without the peptide, the hTRβ LBD precipitated immediately. However, nucleation was erratic, but could be overcome through seeding of prepared drops with microcrystals of the hTRβ LBD:GRIP1 NR-box 2 peptide complex. Structure of the hTRβ LBD:GRIP1 NR-box 2 peptide complex was determined by molecular replacement using the structure of the hTRβ LBD determined previously (Wagner *et al.*, *supra*) and refined to a resolution of 3.6Å (Table 1). The refined model consists of residues K211-P254 and V264-D461 of monomer 1 of the hTRβ LBD, residues K211-P254 and G261-D461 of monomer 2 of the hTRβ LBD, and the GRIP1 NR-box 2 peptides (residues 14-24 of SEQ ID NO: 6) 688-KILHRLLQDSS-698, and (residues 14-22 of SEQ ID NO: 6) 688-KILHRLLQD-696 (Appendix 1). The structure in Appendix 1 consists of: a portion of each of two molecules of hTRβ, chain A (SEQ ID NO: 52) and chain B (SEQ ID NO: 53); two molecules of T_3, chain J and chain K; and two molecules of GRIP-1 peptide, chain X (SEQ ID NO: 54) and chain Y (SEQ ID NO: 55).

Please replace paragraph **[0158]** *as follows*:

Ile 689 from the peptide interacts with three receptor residues (Asp 538, Glu 542 and Leu 539). The γ-carboxylate of Glu 542 forms hydrogen bonds to the amides of residues 689 and 690 of the peptide. A water-mediated hydrogen bond network is formed between the imidazole ring of His 377, the γ-carboxylate of Glu 380, and the amide of Tyr 537. Three residues (Glu 380, Leu 536 and Tyr 537) interact with each other through van der Waals contacts and/or hydrogen bonds. Intriguingly, mutations in each these three residues dramatically increase the transcription activity of unliganded ERα LBD (Eng, *et al.*, *Mol. Cell. Biol.* (1997) 17:4644-4653); Lazennec, et al., *Mol Endocrinol.* (1997) 11:1375-86; White, *et al.*, *EMBO J.* (1997) 16:1427-35). Atomic coordinates of DES-LBD-peptide

complex are attached as Appendix 2. The structure in Appendix 2 consists of: a portion of human ERα, chain A (SEQ ID NO: 56) and chain B (SEQ ID NO: 57); two molecules of DES; and two molecules of GRIP-1 NR-box 2 peptide, chain C (SEQ ID NO: 58) and chain D (SEQ ID NO: 59).

Please replace paragraph **[0160]** *as follows*:

The OHT complex data set was then collected. Starting with one of the monomers of the preliminary low-resolution DES-hERα LBD-NR-box 2 peptide model as the search probe, molecular replacement in AMoRe was used to search for the location of LBD in this crystal form in both $P6_122$ and $P6_522$. A translation search in $P6_522$ yielded the correct solution (R=53.8%, CC=38.2%). In order to reduce model bias, DMMULTI (CCP4, 1994) was then used to project averaged density from the DES complex cell into the OHT complex cell. Using MOLOC, a model of the hERα LBD was built into the resulting density. The model was refined initially in REFMAC and later with the simulated annealing, positional and R-factor refinement protocols in X-PLOR (Brunger, X-PLOR. Version 3.843, New Haven, Connecticut: Yale University, 1996) using a maximum-likelihood target (Adams, *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94:5018-23). Anisotropic scaling and a bulk solvent correction were used and all B-factors were refined isotropically. Except for the R_{free} set (a random sampling consisting of 8% of the data set), all data between 41 and 1.9 Å (with no σ cutoff) were included. The final model consisted of residues 306-551, the ligand and 78 waters. According to PROCHECK (CCP4, 1994), 91.6% of all residues in the model were in the core regions of the Ramachandran plot and none were in the disallowed regions. Thus, the structure of the OHT-hERα LBD complex has been refined against data of comparable resolution (1.90 Å) to a crystallographic B-factor of 23.0% (R_{free} =26.2%). Atomic coordinates of OHT-hERα LBD complex are attached as Appendix 3. The structure in Appendix 3 consists of: atomic coordinates for a portion of human ERα,(SEQ ID NO: 60) complexed with OHT.

In The Claims

Please amend Claims 1 – 8, 12, and 15 to read as follows: